IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF TEXAS
MARSHALL DIVISION

ALLERGAN SALES, LLC, Plaintiff, v. LUPIN LTD., et al., Defendants. AND CONSOLIDATED CASES.	Case No. 2:11-CV-530-JRG **LEAD CASE** Case No. 2:12-CV-175-JRG Case No. 2:12-CV-177-JRG Case No. 2:12-CV-178-JRG

DECLARATION OF VALENTINO STELLA IN SUPPORT OF PLAINTIFF'S CLAIM CONSTRUCTION BRIEF

I, Valentino Stella, declare as follows:

1. I am currently a University Distinguished Professor of Pharmaceutical Chemistry at the University of Kansas, where I have taught courses and directed graduate research in the areas of drug stability, drug formulation, pharmacokinetics, and drug biopharmaceutics.

2. I have an undergraduate degree in pharmacy (1968) from the Victorian College of Pharmacy (now a part of Monash University) in Melbourne, Australia and practiced as a pharmacist for one year prior to entering graduate school in the fall of 1968.

3. I received my doctorate in Analytical Pharmaceutical Chemistry and Pharmaceutics from the University of Kansas in 1971.

4. After receiving my doctorate, I then served as an Assistant Professor at the University of Illinois Medical Center in Chicago from 1971-73 before returning to the University of Kansas, where I have been since 1973.

5. During my time at the University of Kansas, I was the Director for the Center of Drug Delivery Research from 1989 to 1999.

6. I have also been a consultant to the pharmaceutical industry, both to innovator and to generic companies, since 1972, including in the area of ophthalmic drug formulations.

7. I was retained by attorneys for Plaintiff Allergan Sales, LLC to provide technical consultation and expert opinions regarding United States Patents No. 8,008,338 ("the '338 patent"), No. 8,207,215 ("the '215 patent"), and No. 8,377,982 ("the '982 patent") (collectively, the patents-in-suit).

8. In expressing opinions on legal issues, I have applied the following legal standards conveyed to me by Allergan's counsel.

9. I understand that, for claim construction, the claim terms must be interpreted from the perspective of a person of ordinary skill in the art at the time of the invention.

10. In my opinion, a person of ordinary skill in the art for purposes of the patents-in-suit would have been a person with a scientific degree, e.g. Ph.D., M.D., M.S., or B.S., who has at least 2-3 years of experience developing pharmaceutical formulations or treatment methods for the eye or studying or working with ketorolac tromethamine and its characteristics or who has 2-3 years of experience as an ophthalmologist, who has also assisted in developing ophthalmic pharmaceutical formulations or in designing and running clinical trials on such formulations. This person may also work in collaboration with other scientists and/or clinicians who have experience developing ophthalmic pharmaceutical formulations, running clinical trials related to such formulations, and/or treating patients using such formulations.

11. I understand that, when interpreting the meaning of patent claims, it is necessary to do so in light of the intrinsic evidence, including the plain meaning of the claim terms, the

specification, and the prosecution history. When the meaning of a claim term is clear from the intrinsic evidence, there is no need for extrinsic evidence.

12. I understand that, in a patent, there may be both independent claims and dependent claims. Dependent claims must contain all the limitations that are present in the claims from which they depend.

13. In my opinion, the plain meaning of "ketorolac" in the context of ophthalmic drug formulations and the patents-in-suit is ketorolac tromethamine.

14. A person of skill in the art reading the word "ketorolac" in the context of ophthalmic compositions would assume that it is referring to ketorolac tromethamine. Indeed, the only approved ketorolac products in the ophthalmic field use the tromethamine salt of ketorolac. In fact, ketorolac tromethamine is the active ingredient in all the FDA-approved products of any type containing ketorolac.

15. "Ketorolac" is commonly used as shorthand for "ketorolac tromethamine" by those of skill in the art.

16. Claim 1 of the '338 patent recites "[a]n aqueous topical ophthalmic composition comprising 0.4% ketorolac," and claim 10 of the '982 patent recites a "method of treating ocular pain and burning in a person undergoing corneal surgery, the method comprising the step of administering at least once daily to an eye of the person a first composition comprising about 0.4 % w/v ketorolac."

17. In my opinion, the plain meaning of "ketorolac" in these claims, in the context of all the intrinsic evidence, is "ketorolac tromethamine." Similarly, if the term is viewed as "0.4% ketorolac" or "0.4% w/v ketorolac," the plain meaning in the context of all the intrinsic evidence is "0.4% ketorolac tromethamine," or"0.4% w/v ketorolac tromethamine."

18. The patents-in-suit use the terms "ketorolac" and "ketorolac tromethamine" interchangeably, and also use the terms "0.4% ketorolac" and "0.4% ketorolac tromethamine," as well as "0.4% w/v ketorolac" and "0.4% w/v ketorolac tromethamine," interchangeably.

19. Dependent claims 3-5 of the '338 patent, which must contain all the limitations of independent claim 1, use the phrase "0.4% ketorolac tromethamine," which I understand in the context of the patent to mean the same thing as 0.4% ketorolac. Similarly, dependent claim 12 of the '982 patent uses the phrase "0.4% w/v ketorolac tromethamine," which I understand in the context of the patent to mean the same thing as 0.4% w/v ketorolac.

20. Example 1 of the patents describes the preparation of a composition of "0.4% ketorolac tromethamine." Example 3 then describes a clinical study that was performed with the 0.4% ketorolac tromethamine composition prepared according to Example 1.

21. Figures 1-5 all depict results from the clinical study on 0.4% ketorolac tromethamine that is described in Example 3.

22. Figure 1, titled "Effect of Ketorolac 0.4% on Pain Intensity During the First 12 Hours Post-Postoperative Photorefractive Keratectomy (PRK) Surgery," refers to the formulation tested as "ketorolac 0.4%." This plainly is intended to mean the same thing as "0.4% ketorolac tromethamine," which was the only non-vehicle composition that was studied in Example 3. The Figure 1 graph also has bars labeled "Ketorolac" and "Vehicle." The "Ketorolac" bar presents the results for the 0.4% ketorolac tromethamine formulation being studied.

23. The specification's description of Figure 1 says that the figure "shows that pain intensity was significantly less for the subjects who received ketorolac tromethamine 0.4% ($P<0.001$) during the first 12 hours post-PRK compared to those who received the vehicle only."

(Ex. 1, '338 patent at 5:28-31.[1]) Thus, the figure's title refers to ketorolac and the text describing the figure refers to ketorolac tromethamine, further showing that the terms are used interchangeably.

24. Figure 2, titled "Time Course for Achieving 'No Pain' With Ketorolac 0.4% vs Vehicle," also refers to the formulation tested as "ketorolac 0.4%." Again, this is plainly referring to the 0.4% ketorolac tromethamine formulation that was prepared for Example 3. Indeed, Figure 2 also states that "[o]verall $P < .001$ for ***0.4% ketorolac tromethamine*** vs vehicle." Thus, in the same figure, the patent refers to the composition as both "ketorolac 0.4%" and "0.4% ketorolac tromethamine," making clear to a person skilled in the art that the patent is using the terms "ketorolac" and "ketorolac tromethamine" interchangeably.

25. The specification's description of Figure 2 says that the figure "shows that the onset of pain relief was faster with the group that received 0.4% ketorolac tromethamine compared to the group that received the vehicle only." (*Id.*, '338 patent at 5:45-47.) This further shows that the ketorolac 0.4% used in the figure's title refers to 0.4% ketorolac tromethamine.

26. Figure 3, titled "Percentages of Ketorolac 0.4%- and Vehicle-Treated Patients Experiencing Complete or Great Pain Relief Post-PRK," also presents results from the Example 3 study on the 0.4% ketorolac tromethamine composition. Like Figure 1, it uses "ketorolac" and "ketorolac tromethamine" interchangeably.

27. The specification's description of Figure 3 says that the figure "shows that significantly more of the patients who received 0.4% ketorolac tromethamine reported complete or [sic – great] pain relief than vehicle-treated patients throughout the study up to 84 hours."

[1] All exhibits cited are attached to Allergan's Opening Claim Construction Brief.

(*Id.*, '338 patent at 5:55-58.) Again, this shows that the use of the term ketorolac in the title refers to ketorolac tromethamine.

28. Figure 4, titled "Percentages of Ketorolac 0.4%- and Vehicle-Treated Patients Requiring Escape Medication," also presents results from the Example 3 study on the 0.4% ketorolac tromethamine composition. Like Figure 1, it uses "ketorolac" and "ketorolac tromethamine" interchangeably, as further demonstrated by the discussion in the specification. (*Id.*, '338 patent at 5:59-67.)

29. Figure 5, titled "Rate of Re-epitheliazation," also presents results from the Example 3 study on the 0.4% ketorolac tromethamine composition. Figure 5 contains a notation stating that "[o]verall $P = .016$ for ketorolac 0.4% vs vehicle," again using the phrase "ketorolac 0.4%" to refer to the 0.4% ketorolac tromethamine composition being studied.

30. In addition to the figures, Example 3 itself also uses "ketorolac" and "ketorolac tromethamine" interchangeably. Table 4 presents adverse events results for the 0.4% ketorolac formulation that was tested compared to the vehicle. The table refers to the 0.4% ketorolac tromethamine formulation as "Ketorolac 0.4%."

31. Also, the paragraph at the end of Example 3 summarizing the study reads as follows:

> In summary, the 0.4% ketorolac formulation is clinically effective in treating post PRK ocular pain. In comparison with vehicle-treated patients, the 0.4 ketorolac tromethamine-treated patients experienced significantly greater and faster pain relief ($P<0.001$), and used significantly less escape medication compared to vehicle-treated patients ($P \leqq 0.006$). Additionally, the 0.4% ketorolac tromethamine formulation has an excellent tolerability profile. Adverse events were minor and infrequent.

Thus, this paragraph also refers to the formulation tested as both the "0.4% ketorolac formulation" and as the "0.4% ketorolac tromethamine formulation," leaving no doubt that the terms are being used interchangeably.

32. When the term "0.4% ketorolac" is used to refer to the same formulation as "0.4% ketorolac tromethamine," as it is in Example 3, "ketorolac" must refer to the tromethamine salt form rather than the acid form. It could not refer to the acid form of ketorolac because 0.4% of the tromethamine salt of ketorolac is not the same as 0.4% of ketorolac acid, due to differences in the molecular weight of the salt and the acid.

33. The Background of the Invention section of the patents-in-suit also uses the term "ketorolac tromethamine 0.5% (w/v) ophthalmic solution" interchangeably with "0.5% ketorolac formulation." (*Id.*, '338 patent at 1:34-42.) This further demonstrates to a person skilled in the art that the patents use the term "ketorolac" as a shorthand for "ketorolac tromethamine" and use the terms interchangeably.

34. The file histories of the patents-in-suit further support the construction of "ketorolac" to mean "ketorolac tromethamine." During prosecution of the '338 patent, the applicants referred to the Acular® LS products, which contain ketorolac tromethamine, as "the commercial ketorolac" and "the 0.4% ketorolac solution." (Ex. 2 at AGN-ACUL0000065, AGN-ACUL000185, AGN-ACUL0000439-40.) They used a similar shorthand during their oral presentation on appeal. (*Id.* at AGN-ACUL0000452-455.) The applicants also submitted a declaration in which the declarants referred to a 0.4% ketorolac tromethamine solution as "ketorolac." (*Id.* at AGN-ACUL00000246-250.)

35. In addition, the articles and documents submitted during prosecution of the '338 patent, as well as the related patents, further show that those of skill in the art generally referred

to "ketorolac tromethamine" as "ketorolac," and thus also support the construction of "ketorolac" to mean "ketorolac tromethamine." (*See, e.g., Id.* at AGN-ACUL0000071-74, 201-207, e.g. at 201; *Id.* at AGN-ACUL0000067, AGN-ACUL0000284-294.) Indeed, in a summary of Acular® LS submitted to the Patent Office during prosecution, Allergan not only referred to its "0.4% ketorolac tromethamine ophthalmic solution" as "0.4% ketorolac," it also indicated repeatedly in footnotes that "Ketorolac = ketorolac tromethamine." (*Id.* at AGN-ACUL0000253-284, *see, e.g.*, 262.)

36. Therefore, based on both the plain meaning of the term and its use in the specification and the file histories of the patents-in-suit, including the art submitted therein, it is my opinion that a person of ordinary skill in the art would understand that "ketorolac" refers to "ketorolac tromethamine" and "0.4% ketorolac" refers to "0.4% ketorolac tromethamine." Furthermore, the plain meaning of "0.4% w/v ketorolac" in the context of all the intrinsic evidence is "0.4% w/v ketorolac tromethamine."

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Executed this 31st day of May, 2013 at Lawrence, Kansas.

Valentino Stella

CERTIFICATE OF SERVICE

The undersigned certifies that the foregoing document was filed electronically in compliance with Local Rule CV-5(a). As such, this document was served on all counsel who are deemed to have consented to electronic service. Local Rule CV-5(a)(3)(A). Pursuant to Fed. R. Civ. P. 5(d) and Local Rule CV-5(d) and (e), all other counsel of record not deemed to have consented to electronic service were served with a true and correct copy of the foregoing by email, on this 31st day of May, 2013.

/s/ Tamara Fraizer
Tamara Fraizer